UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,496	11/24/1999	MICHELE AGUERA	P06473USO/TP	4418

881 7590 04/09/2003

LARSON & TAYLOR, PLC
1199 NORTH FAIRFAX STREET
SUITE 900
ALEXANDRIA, VA 22314

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/367,496	Applicant(s) AGUERA ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002 and 25 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7,9,10,14,15 and 20-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,9,10,14,15 and 20-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The amendment filed on March 25, 2002 in Paper No. 10 is acknowledged and has been entered. Claims 16 and 17 have been canceled. Claims 1-7, 9, 10, 14, 15, and 20-35 have been amended.

2. The amendment filed on December 2, 2002 in Paper No. 15 is acknowledged and has been entered. Claims 2 and 5 have been canceled. Claims 1, 3, 4, and 30-32 have been amended.

3. Claims 1, 3, 4, 6, 7, 9, 10, 14, 15, and 20-35 are pending in the application and are currently under prosecution.

Election/Restrictions

4. In reply to the previous Office action mailed September 25, 2001, Applicants have requested withdrawal of the restriction requirement. Applicants request is duly noted; however, Applicants elected the invention currently under examination without traverse in Paper No. 8. The restriction requirement is deemed proper because the inventions are distinct for the reasons set forth in the Office action mailed February 13, 2001.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not identify the citizenship of each inventor.

In reply to the preceding Office action, Applicants stated an intention to submit a substitute declaration as soon as the substitute has been executed.

Sequence Rules Compliance

6. The communication filed March 25, 2002 in Paper No. 10 is not fully responsive to the Office communication mailed September 25, 2001 (Paper No. 9) for the reason set forth on the attached Notice To Comply With The Sequence Rules, which is reiterated in the paragraph below. Applicants must comply with the requirements of the sequence rules (37 CFR §§ 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

The amino acid sequence set forth in SEQ ID NO: 8 and the amino acid sequence set forth in Figure 12 are discrepant; yet on, the specification teaches, "Figure 12 represents [...] the inferred amino acid sequence [of ULIP-4 in man] (SEQ ID No: 8)" (page 18, lines 20-22). Thus, the application fails to comply with the sequence rules set forth under 37 CFR §§ 1.821-1.825.

Applicant is given three (3) months from the date of this Office Action within which to comply with the sequence rules under 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Applicant is requested to return a copy of the attached Notice to Comply with the response.

Grounds of Objections and Rejections Withdrawn

7. Unless specifically reiterated below, the grounds of rejection or objection set forth in the previous Office action mailed September 25, 2001 (Paper No. 9) have been withdrawn.

For clarity of record, the grounds of the rejections under 35 USC § 102 and 103 set forth which in the Office action mailed September 25, 2001 in which Hamajima, et al was used as a basis have been withdrawn for the following reason:

The polynucleotide sequence of Hamajima, et al (GenBank Accession No. AB006713) encodes a polypeptide comprising an amino acid sequence that is nearly identical to the amino acid sequence set forth in SEQ ID NO: 8. However, while the polynucleotide sequence of Hamajima, et al encodes lysine at position 56, the sequence encodes arginine at position 122, whereas the amino acid at position 122 in SEQ ID NO: 8 is glutamine.

The grounds of the rejection under 35 USC § 103(a) over Honorat, et al and Antoine, et al, which were set forth in the Office action mailed September 25, 2001, have been withdrawn for the following reason:

Applicants traversed these grounds of rejection arguing that the conclusion of the obviousness of Applicants' claimed invention could only have been reached from an unacceptable hindsight analysis, since Applicants have stated that the anti-CV2 antibodies do not bind the polypeptide if the polypeptide is expressed in *E. coli*. However, the prior art teaches that the antibodies bind the polypeptide if it expressed in human and rat cells, which suggests that the epitope or epitopes of the polypeptide to which the antibodies bind do not form in the absence of post-translation modification. Accordingly, if one of ordinary skill in the art had screened a human brain cDNA library of transformed *E. coli* cells using the anti-CV2 antibodies, there might not have been a reasonable expectation of success in identifying the clone that expresses the polypeptide to which the antibodies bind. For this reason, the grounds of rejection that were set forth in the preceding Office action have been withdrawn and new grounds of rejection under 35 USC § 103 have been set forth herein.

Additionally, it is noted that Applicants stated that while several proteins were found to bind anti-CV2 antibodies, none of the three known ULIP proteins were found to do so. This argument, however, is not persuasive since the prior art teaches that the antibodies bind a 66 kDa polypeptide that is expressed in human brain, and the 66 kDa polypeptide expressed in human brain to which anti-CV2 antibodies bind is the polypeptide of SEQ ID NO: 8. Therefore, with the provision that the polypeptide is isolated from humans cells or expressed in eukaryotic cells, the polypeptide of SEQ ID NO: 8, i.e., ULIP-4, can be readily differentiated from the other members of the ULIP

family of proteins using the anti-CV2 antibodies, so that one of ordinary skill in the art would have had a reasonable expectation of successfully deriving the claimed invention.

Response to Amendment

8. The amendment filed March 25, 2002 in Paper No. 10 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amino acid sequence set forth under SEQ ID NO: 8 of the substitute sequence listing introduces new matter into the disclosure. Presently SEQ ID NO: 8 indicates that the amino acid at position 56 is lysine; however, there is inadequate antecedent basis in the originally filed specification to support the "correction", since the amino acid sequence at position 56 of the original sequence was not lysine. Moreover, while the specification teaches that the amino acid at position 56 of the amino acid sequence of ULIP-4 is almost certainly a lysine, this disclosure is not deemed sufficient to support the alteration of the sequence.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

9. Claim 3 is objected to because of the recitation of "nucleotide" rather than "nucleic". Appropriate correction is required.

10. Claim 4 is objectionable. Claim 3, from which claim 4 depends, recites the limitation requiring the sequence to code "for a ULIP polypeptide of amino acid sequence SEQ ID NO: 8". Therefore, claim 4 is objected to because of the redundant recitation of "coding the ULIP polypeptide of amino acid sequence SEQ ID NO: 8".

11. Claims 23 and 28 are objected to because the claims encompass the subject matter of non-elected inventions. Appropriate correction is required.

12. Claims 24 and 28 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 23 and 25, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Although claim 23 recites the limitation "said antibody capable of forming a specific immunological complex with a ULIP polypeptide", the claims are under examination only insofar as the claims are drawn to the elected invention. Therefore, claims 23 and 24 are substantial duplicates of the other. Similarly, claims 25 and 28 are substantial duplicates of the other.

Claim Rejections - 35 USC § 101

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

This ground of rejection can be rendered moot by amending the claim to recite an active process step.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 3, 4, 6, 7, 9, 10, 14, 15, and 20-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the preceding Office action mailed September 25, 2001 (Paper No. 9).

For the reason set forth in the previous Office action, which has been reiterated above, the teachings of the specification are discrepant. Figure 12 and SEQ ID NO: 8 are disclosed as depicting the same amino acid sequences, but the sequences are not identical. Figure 12 depicts an amino acid sequence in which there is an asterisk at position 56 representing a "stop codon". On the other hand, SEQ ID NO: 8 indicates that a lysine occurs at position 56 within the sequence.

In reply to the previous Office action, Applicants have attempted to resolve this discrepancy by providing a substitute sequence listing, but the discrepancy between the sequence set forth in SEQ ID NO: 8 and the sequence depicted in Figure 12 remains.

Applicants are again invited to resolve the inconsistency, but are cautioned against the introduction of new matter by amending the specification, including the claims.

17. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for using the polypeptide of SEQ ID NO: 8 or derivative thereof to detect the presence of anti-CV2 antibodies in a biological sample, wherein said sample is blood serum or cerebrospinal fluid (CSF), does not reasonably provide enablement for a method for using any fragment of the polypeptide of SEQ ID NO: 8 or a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 7 to detect the presence of anti-CV2 antibodies in any biological sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate

in scope with these claims for the reasons set forth in the Office action mailed September 25, 2001.

Applicants have traversed this ground of rejection arguing that because one skilled in the art could empirically identify a fragment of the polypeptide that binds anti-CV2 antibodies, the methodology is routine and therefore any additional experimentation necessary to have a reasonable expectation of successfully practicing the claimed invention would not constitute an undue amount.

Applicants' arguments have been carefully considered but have not been found persuasive. Contrary to Applicants' assertions, the fact that one skilled in the art would need to empirically identify the fragments of the polypeptide that bind anti-CV2 antibodies before having a reasonable expectation of successfully practicing the claimed invention does not imply that it would be routine to do so, or that the amount of experimentation necessary to do so would not be undue.

Furthermore, although Applicants have pointed to the disclosure of a particular fragment of ULIP-4 in the specification, the claims are not limited to that fragment and moreover the specification does not teach that the fragment binds anti-CV2 antibodies. Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only certain regions of the antigen are antigenic, so that a majority of antibodies produced against an antigen bind to these immunodominant regions of the antigen. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure. As stated in the previous Office action, the skilled artisan cannot predict which fragments of a polypeptide will be antigenic, or which fragments of a polypeptide will bind a particular antibody. This lack of predictability is exemplified by the teachings of Holmes (*Expert Opinion on Investigational Drugs* **10**: 511-519, 2001). Holmes teaches that rabbits were immunized with synthetic peptide fragments of an antigen, which in each case generated highly specific antibodies that bind the peptides; however, none of the antibodies were found to bind the full-length antigen. The author concludes, "[p]resumably, expression of these epitopes in the context of the protein was

important and affected the antibody binding ability (page 513, column 1). Accordingly, peptide fragments of an antigen cannot reliably substitute for the intact antigen in producing antibodies, because the peptide fragments may not reflect the natural tertiary and quaternary structure of antigen.

In addition, as stated in the previous Office action, one skilled in the art would not expect the anti-CV2 antibodies to bind to a nucleic acid comprising the polynucleotide sequence of SEQ ID NO: 7 or for that matter, to any nucleic acid molecule. Furthermore, one skilled in the art would not expect to be able to detect anti-CV2 antibodies in any biological sample. There are numerous examples of tissues in which anti-CV2 antibodies could not be found.

Accordingly, Applicants' arguments have been carefully considered, but have not been found persuasive in view of the preponderance of evidence.

18. Claims 9, 14, 15, and 20-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a composition in a process of diagnosing cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon developing autoimmune disease, wherein said autoimmune disease is characterized by the presence of anti-CV2 auto-antibodies in the serum of patients, wherein said antibodies bind specifically to the polypeptide of SEQ ID NO: 8 and wherein said composition comprises the polypeptide of SEQ ID NO: 8, does not reasonably provide enablement for making and using a composition in a process for diagnosing paraneoplastic neurological syndromes and/or a tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in the Office action mailed September 25, 2001 (Paper No. 9).

The claims are drawn to methods for diagnosing paraneoplastic neurological syndromes or tumors, and to compositions, reagents, and kits useful for doing so.

Applicants have traversed these grounds of rejection arguing that provided a subject expresses anti-CV2 antibodies, the claimed method can be used with a reasonable expectation of success to diagnose any tumor.

Applicants' arguments have been carefully considered but not found persuasive. Firstly, the limitation to which Applicants have referred, namely the provision that the subject express anti-CV2 antibodies, is not recited in the claims. Nevertheless, the specification teaches that the presence of anti-CV2 antibodies is not always indicative of a tumor, since the antibodies were found present in a patient diagnosed with Lambert-Eaton myasthenic syndrome, for example. The skilled artisan could not distinguish a patient having a particular paraneoplastic neurological syndrome characterized by the presence of anti-CV2 auto-antibodies and a patient having a tumor characterized by the presence of the antibodies in the patient's serum. Even so, many tumors have not been associated with the presence of anti-CV2 auto-antibodies in the patient's serum. For example, there is presently no factual evidence that supports the assertion that the claimed invention could be used to diagnose breast cancer, since breast cancer is not known to be associated with the presence of anti-CV2 antibodies.

In view of the preponderance of evidence, Applicants' arguments are not persuasive and therefore the grounds of rejection set forth under 35 USC § 112, first paragraph in the preceding Office action are maintained herein.

19. Claims 3, 6, and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have traversed these grounds of rejection arguing that the disclosure meets the written description requirement set forth under 35 USC § 112, first paragraph. Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Claim 3 is drawn to a nucleic acid molecule comprising a polynucleotide sequence that encodes the amino acid sequence set forth in SEQ ID NO: 8.

The specification teaches the polynucleotide sequence of a complementary DNA (cDNA) molecule that encodes the amino acid sequence set forth in SEQ ID NO: 8. The polynucleotide sequence of the cDNA molecule is set forth in SEQ ID NO: 7.

The disclosure is insufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph, because as stated in the previous Office action, the claims encompass subject matter that is not described in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

In particular, the claims encompass genomic DNA molecules that comprise a polynucleotide sequence that encodes the polypeptide of SEQ ID NO: 8, but the specification only discloses the polynucleotide sequence of a cDNA molecule encoding the polypeptide without disclosing any factual evidence that Applicants had possession of a genomic DNA isolate also encoding the polypeptide. Given only the structure of a cDNA molecule encoding a polypeptide, one skilled in the art cannot envision or even predict the structure of a gene encoding a polypeptide. The structure of a gene can only be determined empirically. Therefore, the disclosure of SEQ ID NO: 7 is not representative of the genus of nucleic acid molecules, including a gene or an allele thereof encoding the polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8 to which the claims are drawn.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires

more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 21 and 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite because the claim recites the limitation "wherein the polypeptide sequence". There is insufficient antecedent basis in claim 20 for recitation of this limitation in claim 21.

Claims 25-29 are vague and indefinite for the reason set forth in the Office action mailed September 25, 2001. Claims 25, 28, and 29 recite the limitation "a tumor of cancerous origin". Generally, a tumor is of cancerous origin. Therefore, the use of the limitation renders the claims vague and indefinite because it is unclear what subject matter the limitation is meant to include and/or what subject matter the limitation is meant to exclude. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 26 is indefinite because the claim recites "wherein the polypeptide comprising amino acid sequence SEQ ID No: 8". The recitation renders the claim indefinite because it cannot be determined whether or how the recitation is meant to limit the subject matter of claim 25.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Antoine, et al (*Journal of Neurological Sciences* 117: 215-223, 1993).

In reply to the previous Office action mailed September 25, 2001, Applicants have stated that claims 30-32 are directed to a diagnostic substrate, i.e., a reagent, for

use in diagnosis and not a method of diagnosis. Applicants have further stated that the claims encompass fixed brain sections.

Antoine, et al teach fixed brain sections that comprise an antigenic portion of a polypeptide endogenous to the brain comprising the amino acid sequence set forth in SEQ ID NO: 8 to which the anti-CV2 antibodies bind.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 9, 10, 14, 15, 20-24, and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honnorat, et al (*Journal of Neurology, Neurosurgery, and Psychiatry* **61**: 270-278, 1996) and Antoine, et al (*Journal of Neurological Sciences* **117**: 215-223, 1993) in view of Stefano, et al (*Cell* **36**: 145-154, 1984), Okajima, et al (*Journal of Biochemistry* (Tokyo) **117**: 980-986, 1995), and US Patent Nos. 5,770,381-A and 6,066,475-A.

Honnorat, et al, Antoine, et al, and US Patent Nos. 5,770,381-A and 6,066,475-A teach that which was set forth in the preceding Office action mailed September 25, 2001.

Stefano, et al teach a method for purifying a polypeptide that binds to an auto-antibody.

Okajima, et al teach a method for isolating a cDNA molecule encoding a polypeptide.

As stated in the preceding Office action, Honnorat, et al and Antoine, et al do not explicitly teach a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind. Honnorat, et al and Antoine, et al do not explicitly teach a method

for diagnosing PNS and/or cancer, wherein said method comprises contacting a biological sample isolated from a patient or other subject with a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind. Honnorat, et al also do not teach a diagnostic kit comprising a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind.

Nevertheless, given the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conclude that the anti-CV2 antibodies of Honnorat, et al bind to a protein expressed in human brain cells, which is approximately the same size as the 66 kDa protein isolated from rat brain cells to which the antibodies bind, because Antoine, et al teach that the antibodies bind both rat brain and human brain and also that the antibodies bind a protein of approximately the same size in both rat brain and human brain. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conclude that protein expressed in the human brain to which the anti-CV2 antibodies bind would be very similar, if not identical to the 66 kDa polypeptide expressed in rat brain to which the antibodies bind, because one of ordinary skill in the art knows that an antibody that has cross-reactivity binds similar or identical antigens expressed in the cross-reactive tissues. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate the polypeptide to which the antibodies bind from the human brain, sequence the polypeptide, at least in part, produce a nucleic acid probe comprising a polynucleotide sequence encoding the polypeptide, and screen a human brain cDNA library to identify a clone comprising a cDNA encoding the polypeptide to which the anti-CV2 antibodies bind, because identification and characterization of the polypeptide is essential to understanding pathology associated with the anti-CV2 antibodies and because conventional and routine methodology could be employed to do so since the rat homologue of the human protein to which the antibodies bind had already been isolated and characterized. Nevertheless, Stefano, et al teach a method by which the antigen to which an auto-antibody binds can be purified and given a purified protein, Okajima, et al teach a method by which a cDNA molecule encoding the protein can be isolated. One

of ordinary skill in the art, thus, would have been motivated to isolate the polypeptide to which the antibodies bind from the human brain, sequence the polypeptide, at least in part, produce a nucleic acid probe comprising a polynucleotide sequence encoding the polypeptide, and screen a human brain cDNA library to identify a clone comprising a cDNA encoding the polypeptide to which the anti-CV2 antibodies bind, because a cDNA encoding the polypeptide could be used to gain an understanding of the pathology associated with anti-CV2 antibodies and of course, to produce the polypeptide, which could be used as a tool in further experimentation aimed at this goal. Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to clone the human cDNA molecule, because based upon the teachings of Honnorat, et al, in particular, one of ordinary skill in the art at the time the invention was made would have had the additional incentive that the polypeptide produced by the isolated human cDNA could be used to develop a diagnostic protocol, wherein a patient could be diagnosed with cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, wherein the development of said pathology in the patient is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, because Honnorat, et al teach that the detection of anti-CV2 antibodies is indicative of said pathologies.

In view of the teachings of Honnorat, et al, Antoine, et al, and the teachings of US Patents Nos. 5,770,381-A and 6,066,475-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have isolated a clone comprising a cDNA molecule encoding the polypeptide expressed in human brain to which the anti-CV2 antibodies bind by a process according to Stefano, et al and Okajima, et al. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the polypeptide, developed a diagnostic assay for diagnosing cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, wherein the development of said pathology in a patient is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence of anti-CV2

autoantibodies in the serum of the patient, and produced a kit comprising the polypeptide or a composition comprising the polypeptide or a solid support comprising the polypeptide, because the combined teachings of Honnorat, et al, Antoine, et al, and US Patents Nos. 5,770,381-A and 6,066,475-A would have provided one of ordinary skill in the art with sufficient guidance in view of conventional knowledge in the art to do so and also would have provided one of ordinary skill in the art with sufficient incentive to do so. In particular, Honnorat, et al and Antoine, et al teach that the presence of anti-CV2 antibodies is diagnostic of cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton syndrome and US Patents Nos. 5,770,381-A and 6,066,475-A teach that the polypeptide to which autoantibodies bind can be used as diagnostically, but it is further noted that there had been a long-felt need in the art for better diagnostic assays, which could be used to diagnose pathologies associated with the development of autoantibodies, namely anti-CV2 antibodies.

26. Claims 15 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamajima, et al (*Gene* **180**: 157-163, 1996), as evidenced by GenBank Accession No. AB006713 (USPTO search report US-09-367-496-8.std.rge).

Hamajima, et al teach a purified polypeptide comprising an antigenic portion of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8 or a derivative thereof, which is, itself, a means of visualizing formation of a immune complex of an antibody and a polypeptide comprising said antigenic portion. Additionally, Hamajima, et al teach the polypeptide is expressed in animal brain.

However, Hamajima, et al do not teach a kit comprising a purified polypeptide comprising an antigenic portion of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8 or a derivative thereof. Furthermore, Hamajima, et al do not teach the provision of a reagent, namely animal brain.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to manufacture and use a kit comprising the purified polypeptide of Hamajima, et al because the polypeptide could be used experimentally and kits provide greater ease, convenience, and uniformity. For example, the

polypeptide could be used as an immunogen to produce an antibody that binds the polypeptide, or the polypeptide could be used to purify an antibody that binds the polypeptide by affinity chromatography; and a kit comprising the polypeptide would have provided the scientific investigator with a convenient and uniform source of the polypeptide. One of ordinary skill in the art at the time the invention was made would have been motivated to manufacture and use such a kit for the same reasons that it would have been obvious to do have done so, namely because of the greater ease, convenience, and uniformity that kits were known to provide.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to procure a section or sample of an animal's brain for use as a reagent comprising the polypeptide of Hamajima, et al because Hamajima, et al teach the polypeptide is expressed in animal brain. One of ordinary skill in the art at the time the invention was made would have been motivated to procure such a reagent because the reagent could have been used to study the expression of the gene encoding the polypeptide, or it could have been used to study the function of the polypeptide.

Conclusion

27. No claims are allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 26, 2003

Notice to Comply	Application No.	Applicant(s)	
	09/367,496	AGUERA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: This application fails to currently fails to comply because of discrepancy between the disclosure and the seqeunce listing, as indicated in the previous Office action; additionally, the sequence depicted in Figure 12 is not included in the present sequence listing. Applicant must take appropriate actions to correct the deficiencies.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY